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Author Statement

Yingxue Liu: Investigation, Formal analysis, Writing- Original draft preparation

Kai Liu: Writing - Review & Editing

Ping Zheng: Visualization

Shanshan Yin: Formal analysis

Hangbiao Jin: Methodology, Writing - Review & Editing

Xiaoxia Bai: Sample collection

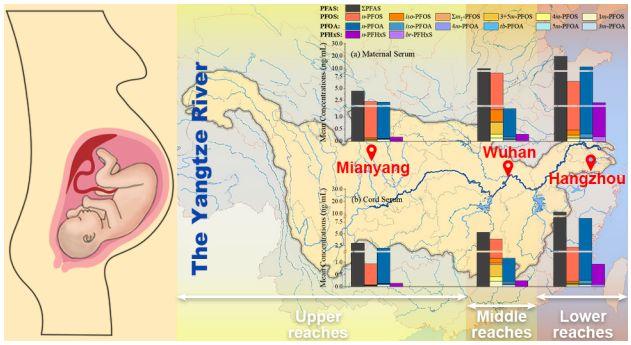
Yongqing Li: Sample collection

Jingxian Zheng: Sample pretreatment experiments

Yishuang Dai: Sample pretreatment experiments

Meirong Zhao: Project administration

Weiping Liu: Supervision, Resources, Funding acquisition



Prenatal exposure and transplacental transfer of perfluoroalkyl substance isomers in participants from the upper and lower reaches of the Yangtze River

Yingxue Liu,[a] Kai Liu,[b] Ping Zheng,[a] Shanshan Yin,[a] Hangbiao Jin,[c] Xiaoxia Bai,[d] Yongqing Li,[e] Jingxian Zheng,[a] Yishuang Dai,[a] Meirong Zhao,[c] Weiping Liu,[*, a]

[a] Ministry of Education Key Laboratory of Environmental Remediation and Ecosystem Health, Institution of Environmental Health, Zhejiang University, Hangzhou, 310058, China

[b] Division of Engineering and Applied Science, W. M. Keck Laboratories California Institute of Technology, 1200 East California Blvd., Pasadena, California 91125, USA

[c] Key Laboratory of Microbial Technology for Industrial Pollution Control of Zhejiang Province, College of Environment, Zhejiang University of Technology, Hangzhou 310058, China

[d] Women Hospital, School of Medicine, Zhejiang University, Hangzhou 310058, China

[e] Mianyang Municipal Center for Disease Control and Prevention, Mianyang 621000, China

[*] Corresponding Author

Prof. Dr. Weiping Liu, Institution of Environmental Health, Zhejiang University. E-mail address: wliu@zju.edu.cn

ABSTRACT: Data on gestational exposure characteristics and transplacental transfer are quite limited for perfluoroalkyl substance (PFAS) isomers, especially those from large-scale comparative studies. To fill this gap, we examined isomers of perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and perfluorohexane sulfonic acid (PFHxS) in matched maternal and cord serum from Mianyang and Hangzhou, which are located in the upper and lower reaches of the Yangtze River, China, respectively. These data were compared with those from our previous study on Wuhan in the middle reach. The average ΣPFAS concentrations increased from upstream to downstream (Mianyang (4.44 ng/mL) < Wuhan (9.88 ng/mL) < Hangzhou (19.72 ng/mL)) and may be related to the per capita consumption expenditures of each city. The ln-transformed PFAS concentrations showed significant differences between Mianyang and Hangzhou after adjusting confounding factors ($p < 0.05$). The percentages of linear PFOS and PFOA in maternal and cord serum from these cities all exceeded those in electrochemical fluorination products. The isomer profiles of PFASs in maternal and cord serum might be greatly influenced by local production processes of PFASs and residents' dietary habits. The transplacental transfer efficiencies decreased significantly with increasing concentrations in maternal serum for ΣPFAS, ΣPFOS, ΣPFOA, ΣPFHxS, *n*-PFOS, *iso*-PFOS, 4*m*-PFOS, 1*m*-PFOS, *n*-PFOA, *n*-PFHxS, and *br*-PFHxS (Spearman rank correlation coefficients (r) = 0.373−0.687, $p < 0.01$). These findings support an understanding of the regional characteristics in maternal exposure to PFASs along the Yangtze River, isomeric profiles of PFASs in these regions, and the transplacental transfer processes of PFAS isomers.

Capsule: Prenatal PFAS exposure was lowest in Mianyang, then higher in Wuhan, and highest in Hangzhou, from the upper to the lower reaches of the Yangtze River.

Keywords: PFOS, PFOA, PFHxS, isomers, transplacental transfer, the Yangtze River

1. Introduction

Poly- and perfluoroalkyl substances (PFASs) are a class of anthropogenic chemicals with different fluorinated alkyl chains (C_nF_{2n+1}-) and polar functional groups (de Voogt and Sáez, 2006). Among these compounds, perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and perfluorohexane sulfonic acid (PFHxS) have become pollutants of interest for decades because of their persistence (Giesy and Kannan, 2002), bioaccumulation (Hansen et al., 2001), potential harmfulness to humans (UNEP, 2007), prevalent industrial use (Prevedouros et al., 2006), and wide global distribution (Giesy and Kannan, 2002). The primary industrial processes to produce PFASs include electrochemical fluorination (ECF) and telomerization. Amongst them, ECF usually results in branched by-products. For example, ratios of linear isomers to branched isomers are approximately 70:30 and 78:22 for ECF production of PFOS and PFOA, respectively (Beesoon et al., 2011; Prevedouros et al., 2006). On the other hand, telomerization primarily or exclusively produces linear PFASs (Buck et al., 2011), and it has become the predominant PFOA production process. As a result, isomeric fingerprints of PFASs in the human body might provide important information on exposure sources.

Prenatal exposure to these pollutants is of great concern, as pregnant women and fetuses are particularly vulnerable to xenobiotic exposure (Roze et al., 2009). It has been reported that PFASs have potential adverse impacts on maternal fecundity (Velez et al., 2015), pregnancy-induced hypertension (Darrow et al., 2013), neonatal birth outcomes (Govarts et al., 2018; Johnson et al., 2014), gestational age (Arbuckle et al., 2013; Chen et al., 2012), and so on. Compared with linear PFOS, prenatal exposure to branched PFOS may have a greater impact on infant birth weight (Li et al., 2017). As the toxicological effects and biological behaviors of these compounds are

47 expected to have an origin in their molecular structure and may differ considerably among isomers,
48 studies on the differences in prenatal exposure among PFASs at isomeric levels are very important.
49 PFASs can be transferred from mothers to fetuses via the placenta (Zhang et al., 2013a). The
50 human placenta is a complex structure that includes the amnion, chorion, and basal plate (Sood et
51 al., 2006). It is essential for the material exchange between the mother and fetus. Within the
52 placenta, the apical and basal membranes of syncytiotrophoblasts as well as fetal capillary
53 endothelia have different transporters that can either uptake or efflux xenobiotics (Vahakangas and
54 Myllynen, 2009). It has been suggested that the expression of a transport protein in the placenta,
55 organic anion transporter 4 (OAT 4), decreases the transplacental transfer of PFOA and
56 PFOS (Kummu et al., 2015). This indicates that the expression of various transporters in the
57 placenta may play an important role in the transplacental transfer of PFASs. But the transplacental
58 transfer mechanism of PFASs remains unclear.
59 To date, only two studies have investigated the transplacental transfer efficiencies of
60 individual isomers of PFASs from maternal to cord serum (Beesoon et al., 2011; Chen et al., 2017).
61 The transplacental transfer efficiencies of PFOS isomers declined with increasing distance of the
62 branching point from the sulfonate moiety. While branched isomers could cross placentae more
63 efficiently than the linear isomer for both PFOS and PFOA, the opposite trend was observed for
64 PFHxS (Beesoon et al., 2011; Chen et al., 2017). More explorations are warranted because
65 studying the transplacental transfer process of PFAS isomers is important for understanding the
66 placental function, evaluating the uterine environment, and protecting fetal health.
67 To date, the geographical diversity in the prenatal exposure of PFAS isomers has not been
68 reported, while such information helps us to better understand macroscopic exposure trends,
69 exposure sources, influence factors, and transfer processes. In China, three cities along the Yangtze
70 River, Mianyang (in Sichuan Province), Wuhan (in Hubei Province), and Hangzhou (in Zhejiang

Province), are located in the upper, middle, and lower reaches, respectively. For this river, PFASs have been detected in the water (Pan et al., 2014) and fish (Liu et al., 2018). PFASs in water was related to cities' gross domestic product (GDP) per capita (Piao et al., 2017). PFAS isomers in food, such as fish, could affect isomeric profiles of PFASs in human bodies (Shan et al., 2016). The economic levels and residents' eating habits among the cities along the Yangtze River are different (Table S1 and Figure S1). But it is still unclear whether human PFAS exposure along this river show certain trends or differences due to these economic and dietary differences.

In the current study, isomers of PFOS, PFOA, and PFHxS were quantified in paired maternal serum and cord serum collected from Hangzhou (n = 36) and Mianyang (n = 36). Data on samples from Wuhan (n = 32) from our previous study were cited for comparison (Chen et al., 2017). The objectives of this study are to (i) investigate the exposure discrepancies and trends of PFASs among cities in the upper, middle, and lower reaches of the Yangtze River, (ii) analyze isomer profiles of PFASs in maternal and infant populations and identify key influence factors, and (iii) explore the transplacental transfer processes of PFAS isomers and explain our findings.

2. Materials and methods

2.1. Study Population and Sample Collection

We recruited 36 pregnant women between January 2018 and May 2018 in Mianyang, Sichuan Province, China, as well as 36 pregnant women between April 2019 and June 2019 in Hangzhou, Zhejiang Province, China. None of these pregnant women and their babies had a serious illness. All babies were singleton births without congenital problems. All pregnant women from Mianyang had lived there for more than a decade, and all pregnant women from Hangzhou had no residence history in other places before delivery. Their umbilical cord blood was collected at delivery, and

matched maternal blood was collected near delivery for studying the transplacental transfer efficiency. Once these blood samples had been collected, they were immediately separated by centrifugation at 5000 rpm for 10 min to obtain serum on-site. All samples were stored in sterile polypropylene tubes and frozen at −80 °C. The demographic information of the mothers and neonates is listed in Table S2. For comparative purposes, we have cited the PFAS concentrations in 32 pairs of maternal and cord serum that were collected at Wuhan, Hubei Province, China. These results were reported in our previous study (Chen et al., 2017). All participants provided written informed consent. The ethical protocol was approved by the ethics committees of the Mianyang Maternal and Child Health Center.

2.2. Standards and Reagents

The naming of isomers of PFOA, PFOS, and PFHxS followed the nomenclature proposed by Benskin et al. (Benskin et al., 2007). The following standards were purchased from Wellington Laboratories Inc. (Ontario, Canada): individual standards of *n*-, 1*m*-, 3*m*-, 4*m*-, 5*m*-, *iso*-, (4,4) m_2-, (4,5) m_2-, and (5,5) m_2-PFOS (i.e., *tb*-PFOS); individual standards of *n*-, 3*m*-, 4*m*-, 5*m*-, *iso*-, (4,4) m_2-, (4,5) m_2-, and (5,5) m_2-PFOA (i.e., *tb*-PFOA); a mixture of *n*-/*br*-PFHxS; and isotopically labeled standards of $^{13}C_4$-PFOS, $^{13}C_8$-PFOS, $^{13}C_4$-PFOA, $^{13}C_8$-PFOA, and $^{18}O_2$-PFHxS. Optimal LC/MS-grade methanol, ammonium hydroxide (NH_4OH), ammonium acetate, and formic acid were obtained from Fisher Scientific Inc. (Loughborough, UK).

2.3. Sample Extraction

Solid phase extraction (SPE) was used for the simultaneous determination of target linear and branched PFAS isomers in serum samples as described in our previous study (Chen et al., 2017). In brief, 1 mL of serum was first spiked with isotopically labeled internal standards, namely,

$^{13}C_4$-PFOS, $^{13}C_4$-PFOA, and $^{18}O_2$-PFHxS. After adding 3 mL of 0.1 M formic acid, the mixture was vortexed and then sonicated for 20 min. SPE was conducted using Oasis-HLB cartridges (Waters, Milford, MA; 60 mg/3 mL). Before each extraction run, the extractor lines were washed with methanol and water, and the cartridges were conditioned with methanol (2 mL) and 0.1 M formic acid (2 mL). Next, the samples were passed through the cartridges at 1 mL/min. These cartridges were then washed with 0.1 M formic acid (3 mL), a mixture of 0.1 M formic acid and methanol (1:1, v/v, 5 mL), and 1% NH_4OH/water (1 mL). Afterward, the analytes were eluted from the cartridges with 1 mL of 1% NH_4OH/methanol. The above eluates were concentrated under a gentle stream of nitrogen and then reconstituted with a mixture of 250 µL of methanol and 250 µL of Milli-Q water. The extracts were centrifuged at 10000 rpm, and the supernatants were collected into polypropylene vials (Agilent Technologies, Santa Clara, CA). Finally, the extracts were spiked with injection internal standards ($^{13}C_8$-PFOS and $^{13}C_8$-PFOA) prior to analysis.

2.4. Instrumental Analysis

Isomers of PFOS, PFOA, and PFHxS were quantitatively determined by an Ultra Performance Liquid Chromatography coupled with Xevo TQ-S triple quadrupole mass spectrometry system (Waters ACQUITY UPLC I-Class, Milford, MA). A Fluoro Sep RP Octyl column (2.1 mm × 150 mm, 3 µm, ES Industries) was used for isomeric separation of PFASs based on the methods developed by Benskin et al. (Benskin et al., 2007) The gradient elution was at 200 µL/min, starting with 50% solvent A (5 mM ammonium formate in water at pH 4.0 adjusted by formic acid) and 50% solvent B (100% methanol). The settings of the mobile phase gradient were as follows: 0.0 min, 50% B; 0.3–1.9 min, 64% B; 1.9–5.9 min, 66% B; 5.9–7.9 min, 70% B; 7.9–40 min, 78% B; 40–41 min, 100% B; 41–46 min, 100% B; 46–47 min, 50% B; and 47–60 min, 50% B. Parameters of negative electrospray ionization mode were as follows: capillary voltage, 3 kV; desolvation temperature,

400 °C; desolvation gas flow, 1000 L/h; and collision gas flow and cone gas flow, 0.15 mL/min and 150 L/h, respectively. The precursor and product ions and relevant parameters for target analytes are provided in Table S3.

2.5. Quality Assurance/Quality Control

The internal-standard method was conducted to quantify the concentrations of PFAS isomers in serum. A procedural blank using Milli-Q water was set up with each batch of twelve samples to monitor the potential background contamination. The average matrix spiking recoveries (80–111%) and standard variations are shown in Table S4. The method quantification limit (MQL) is also available in Table S4, which was defined as the concentration responding to a signal-to-noise ratio of ten in the serum matrix. All labware was polypropylene and rinsed with HPLC-grade methanol (Sigma-Aldrich) twice before use.

2.6. Data Analysis

The transplacental transfer efficiency was estimated by calculating the ratio (R_{CM}) of PFAS concentrations in the cord serum (C_{cord}, ng/mL) to those in the paired maternal serum ($C_{maternal}$, ng/mL). The percentages or means (standard deviations) were calculated for the descriptive statistical analyses of PFAS isomer levels and participant characteristics. Only compounds that were detected in more than 33.3% of samples were included in the statistics. PFAS concentrations in maternal and cord serum below MQL were substituted by MQL/2 in calculating the mean concentrations but were treated as missing values in the calculation of R_{CM} for paired samples.

Data were evaluated for normality using the Kolmogorov−Smirnov test. The concentrations of PFASs were ln-transformed to gain normal distributions. Correlations were estimated by the Pearson correlations coefficients if two sets of data were both in normal distribution; otherwise,

the Spearman rank correlation coefficients were used. Differences were estimated by the Paired Sample T-test (for two sets of data in pairs), the Independent Sample T-test (for two sets of independent data), or the One-way Analysis of Variance (for three or more sets of independent data) if data were in normal distribution; otherwise, the Wilcoxon Signed-Rank Test (for paired data) or the Mann-Whitney U Test (for independent data) were used.

Univariate and multivariable linear regressions were conducted to compare the differences in PFAS exposure between Hangzhou and Mianyang. The ln-transformed PFAS concentrations were set as dependent variables, and city was set as the predictor variable. No confounding variables were introduced to the crude model (Model 1). Maternal age, gestational age, pregnancy times, degree of education, occupation, and address were confounding variables in the basic adjusted model (Model 2) because they were significantly different between two cities, linearly correlated with ln-transformed concentrations of most PFASs, and not multiple collinear (VIF < 5). In the further adjusted model (Model 3), in addition to the above confounding variables, more factors were added, including blood type, parity, maternal height, maternal weight, neonatal gender, birth weight, and birth length (VIF < 5). All the statistical significance level was at $\alpha = 0.05$. All statistical tests were performed using SPSS Statistics software version 20.0 (IBM, Chicago, IL, USA).

3. Results

3.1. Exposure Levels and Discrepancies of PFASs in Participants from Mianyang, Wuhan, and Hangzhou

The frequency of detection and average concentrations of PFAS isomers in maternal serum and cord serum in Mianyang, Hangzhou, and Wuhan are shown in Table S5. 1*m*-PFOS (94−100%),

4*m*-PFOS (28−100%), 3+5*m*-PFOS (81−100%), *n*-PFOS (100%), *iso*-PFOS (75−100%), *n*-PFOA (100%), *n*-PFHxS (86−100%), and *br*-PFHxS (31−100%) showed relatively high frequencies of detection in maternal and cord serum from these three cities. The detection frequencies of 5*m*-PFOA (0−33%), 4*m*-PFOA (0−6%), and *tb*-PFOA (0%) were quite low. Σm_2-PFOS and 3*m*-PFOA showed high detection rates in Wuhan but low detection rates in Hangzhou and Mianyang.

The average concentrations of PFOS, PFOA, and PFHxS isomers in Mianyang, Hangzhou, and Wuhan are illustrated in Figure 1. The average total concentrations of PFASs in serum followed the sequence of Mianyang (4.44 ng/mL) < Wuhan (9.88 ng/mL) < Hangzhou (19.72 ng/mL), gradually increasing from upstream to downstream. The average ΣPFHxS concentrations followed the same sequence in maternal serum and cord serum. However, the average concentration of ΣPFOS in Wuhan surpassed that in Hangzhou and Mianyang, while the average concentration of ΣPFOA in Wuhan was much lower than that in the other two cities. In all accounts, the average concentrations of ΣPFOS, ΣPFOA, and ΣPFHxS in Hangzhou were always greater than those in Mianyang.

The concentration box plot of the 144 samples from Hangzhou and Mianyang is illustrated in Figure S2. The maternal serum concentrations of ΣPFOS, ΣPFOA, and ΣPFHxS showed significant ($p < 0.01$) discrepancies between Mianyang and Hangzhou. The discrepancies were also significant ($p < 0.01$) in cord serum. After adjusting confounding factors in Model 2, the factor “city” still showed a significant impact on the ln-transformed PFAS concentrations in maternal and cord serum (Table S6). The further adjusted model (Model 3) also showed significant differences in ln-transformed PFAS concentrations (except for 4m-PFOS) between Mianyang and Hangzhou.

Between maternal and cord serum, the mean concentrations of ΣPFOS, ΣPFOA, and ΣPFHxS in the former all exceeded those in the latter for all three cities (Figure 1). These differences were all significant ($p < 0.01$) in Hangzhou. For Mianyang, the differences were significant ($p < 0.01$) for ΣPFOS and ΣPFHxS but insignificant for ΣPFOA ($p > 0.05$).

3.2. Isomer Profiles of PFOS, PFOA, and PFHxS in the Three Cities

The isomer compositions of PFASs in Mianyang, Hangzhou, and Wuhan are illustrated in Figure 2. The median proportions of *n*-PFOS in maternal and cord serum in these cities all exceeded that in historical ECF PFOS products (approximately 70%). The median percentages of *n*-PFOS in Wuhan (76–84%) were lower than that in Hangzhou (92–94%) and Mianyang (91–93%) in both the maternal and cord serum. Percentages of *n*-PFOS in maternal serum were significantly higher than those in cord serum in both Mianyang and Hangzhou ($p < 0.01$), as listed in Table S7.

For PFOA, branched isomers contributed 10–11% in Wuhan, 2–3% in Hangzhou, and 7% in Mianyang in the maternal and cord serum. The median proportions of *n*-PFOA were higher than those in historical ECF PFOA products (approximately 78%) in these three cities. Hangzhou showed higher n-PFOA% in both maternal and cord serum than Mianyang ($p < 0.01$). The discrepancies in n-PFOA% in maternal and cord serum were significant in Hangzhou ($p < 0.01$) but inconspicuous in Mianyang ($p = 0.059$).

In terms of PFHxS, the branched compositions accounted for 9–10% in Hangzhou and 2–4% in Mianyang ($p < 0.01$ for both maternal and cord serum), where the median percentages in maternal serum slightly surpassed those in cord serum ($p < 0.05$ in Mianyang, $p > 0.05$ in Hangzhou). In Wuhan, *br*-PFHxS accounted for 14% of the PFHxS concentration in maternal serum but only 3% in cord serum, which was quite different from the other cities.

3.3. Transplacental Transfer Efficiencies of PFAS Isomers

Correlations between ln-transformed concentrations of PFOS, PFOA, and PFHxS isomers in the paired maternal serum and cord serum samples in Mianyang and Hangzhou are shown in Table S8. For 1*m*-PFOS, 4*m*-PFOS, 3+5*m*-PFOS, *n*-PFOS, *iso*-PFOS, *n*-PFOA, *iso*-PFOA, *n*-PFHxS, and *br*-PFHxS, with detection rates of more than 33.3% in paired maternal serum and cord serum, significant positive correlations ($p < 0.01$) were found in Mianyang ($n = 36$), Hangzhou ($n = 36$), and both cities ($n = 72$).

Transplacental transfer efficiencies of isomer-specific PFASs in samples from Mianyang and Hangzhou are illustrated in Figure 3. The average R_{CM} of PFOS isomers followed the sequence of 1*m* > 4*m* > 3+5*m* > *n* > *iso*. For PFOA, the R_{CM} ranked as *iso* > *n*. Regarding PFHxS, the average R_{CM} of *br*-PFHxS exceeded that of the linear isomer. As shown in Table S9, the differences of ln-transformed R_{CM} among PFOS isomers were all significant ($p < 0.05$), except for the difference between 4*m*-PFOS and 3+5*m*-PFOS. In terms of PFOA, the difference between *iso*-PFOA and *n*-PFOA was significant ($p < 0.01$). But the difference between *n*-PFHxS and *br*-PFHxS was not significant ($p > 0.05$).

For different PFAS concentrations in mothers, the transplacental transfer efficiencies were not constant but had a significant correlation with the concentration. As shown in Table 1, R_{CM} values decreased with the increase of the corresponding concentrations in maternal serum for 1*m*-PFOS, 4*m*-PFOS, *n*-PFOS, *iso*-PFOS, *n*-PFOA, *n*-PFHxS, *br*-PFHxS, ΣPFOS, ΣPFOA, ΣPFHxS, and ΣPFAS ($p < 0.01$). In cord serum, these correlations were only significant for *n*-PFOA, *n*-PFHxS, *br*-PFHxS, ΣPFOA, and ΣPFHxS ($p < 0.05$).

4. Discussion

4.1. Internal Exposure Levels of PFASs and their Discrepancies among Mianyang, Wuhan, and Hangzhou

To compare the internal exposure levels of PFASs in the present study with those in other parts of the world, we refer to our previous review article that summarized the concentrations of PFASs in maternal and cord blood around the world (Liu et al., 2020). Median ΣPFOS concentrations worldwide ranged from 1.6 ng/mL (Hanssen et al., 2010) to 19.7 ng/mL (Needham et al., 2011) in maternal serum and from 0.76 ng/mL (Lee et al., 2016) to 6.6 ng/mL (Needham et al., 2011) in cord serum, including those in Hangzhou (6.00 ng/mL in maternal serum and 1.80ng/mL in cord serum) and approximating those in Mianyang (1.91 ng/mL in maternal serum and 0.73 in cord serum). Since the ΣPFOS concentrations were relatively low in Mianyang, the corresponding concentrations of PFOS isomers in Mianyang were also slightly lower than those in other studies (Chen et al., 2017; Jiang et al., 2014; Li et al., 2017; Wang et al., 2018b; Zeng et al., 2019; Zhang et al., 2017). Whereas, the concentrations of PFOS isomers in Hangzhou were similar to those in these studies. Regarding ΣPFOA, the median or mean concentrations in both maternal and cord serum worldwide were mainly in the range of 1 to 3 ng/mL. Those in Mianyang were also in this range. The concentrations in Hangzhou were higher than this common range, but they were far below the 42.83 ng/mL in maternal serum and 34.67 ng/mL in cord serum reported in Shandong Province, China (Wang et al., 2019; Yao et al., 2019). Besides, The average levels of n- or iso-PFOA in Hangzhou were also higher than most of the other reported values (Chen et al., 2017; Jiang et al., 2014; Li et al., 2017; Wang et al., 2018b; Zeng et al., 2019; Zhang et al., 2017). As for ΣPFHxS, with the exception of Guangzhou, China (Li et al., 2017; Zhang et al., 2017), Uppsala, Sweden (Karrman et al., 2007), and the Faroe Islands (Needham et al., 2011), the mean or median concentrations reported worldwide were usually lower than 2 in maternal serum and lower than 1

in cord serum (Liu et al., 2020). In both Mianyang and Hangzhou, the average concentrations of ΣPFHxS in maternal and cord serum were in this range too. The br-PFHxS concentrations in maternal or cord serum had only been reported in Wuhan, and these values were close to and between those in Mianyang and Hangzhou.

The order of ΣPFAS exposure levels from upstream to downstream of the Yangtze River Basin may be related to the economic and consumption levels of these cities. Previous studies have reported significant positive correlations between PFAS concentrations in maternal plasma and annual household income (Lewin et al., 2017; Tsai et al., 2018) and between PFAS concentrations in water and GDP per capita of cities or prefectures (Piao et al., 2017). However, the proportion of the secondary industry that has a greater impact on PFAS pollution contributed differently to GDP among cities, and consumption levels may better reflect the use of products that contain PFASs than income. Therefore, in the present study, we investigated the relationship between internal exposure levels of ΣPFAS and per capita consumption expenditures. We found that they followed the same sequence: Mianyang < Wuhan < Hangzhou (Table S1). According to the statistics of the Chinese Government in 2018, daily living (food, tobacco, wine, clothing, and daily necessities and services) accounted for approximately 41.1% of the national per capita consumption expenditure in 2018, which was the predominant area of household consumption expenditure (China State Council, 2018). In daily living, PFOS (UNEP, 2009), PFOA (UNEP, 2019), and PFHxS (UNEP, 2018) are widely used in a variety of consumer goods, including textiles, leather, apparel, paper, carpets, packaging materials, nonstick kitchenware, coatings and so on. These civilian products penetrate our daily lives and cause direct or indirect exposure to PFASs. It has been found that the use of cosmetics, care products, nonstick-coated cooking utensils (Kang et al., 2016), and carpeting (Beesoon et al., 2012; Harris et al., 2017) were predictors of higher PFAS concentrations in the human body. Food packaging (Susmann et al., 2019), microwave paper packaging (Brenes et

296 al., 2019), outdoor apparel (Hill et al., 2017), and waterproof and oil-resistant high-grade clothing
297 may also increase people's exposure to PFASs. Impregnation sprays, treated carpets in homes, as
298 well as coated food contact materials might be the main consumer products that increase exposure
299 to PFOS and PFOA (Trudel et al., 2008). The improvement of consumption expenditure levels is
300 likely to promote the widespread consumption of the above products containing PFASs, thereby
301 increasing the overall exposure of ΣPFAS to the local maternal and infant populations.
302 Regional pollution characteristics may cause extremely high concentrations of certain PFASs
303 in the macroscopic environment, thereby affecting human exposure levels. Hangzhou is a
304 well-known papermaking industrial base with severe pollution of PFOA (Lu et al., 2017; Piao et
305 al., 2017); Wuhan has been a famous production base of the fluorochemical industry since the
306 1960s with a tremendous amount of PFOS detected in dust (Wang et al., 2010). Comparing the
307 concentrations of PFOS and PFOA in the water in these cities, we found that the PFOA
308 concentration (mean: 85 ng/L) greatly surpassed PFOS (mean: 2.3 ng/L) in the surface water of
309 Hangzhou (Lu et al., 2017); in the surface water of Wuhan, the PFOS concentration (Geomean: 4.9
310 ng/L) exceeded the PFOA concentration (Geomean: 3.5 ng/L) (Jin et al., 2006); in the tap water of
311 Mianyang, the concentration of PFOS was very close to that of PFOA (Fang et al., 2018). These
312 distributions were in line with the results in the present study, where PFOA was predominant in
313 Hangzhou, PFOS was the highest in Wuhan, and PFOA was similar to PFOS in Mianyang in terms
314 of the concentrations in maternal serum. As for PFHxS, its level was highest in Hangzhou,
315 followed by Wuhan and Mianyang in sequence. Among the various applications of PFHxS, the use
316 in textile finishing constituted around 22% in the world market in 2016, second only to that in
317 firefighting foams (around 66%) (NEA, 2018). The textile and chemical fiber industry was the
318 pillar industry and occupied the largest proportion of the total industrial economy in Hangzhou,
319 which might account for the relatively high exposure to PFHxS in Hangzhou (LHOH, 2019). For

the parent compound of PFHxS, perfluorohexane sulfonyl fluoride (PFHxSF), its applications were mainly comprised of intermediate feedstock (43%), textiles (10%), electronics/semiconductors (8%), coatings (5%), packaging (5%), and others for the world market (NEA, 2018). Consumption of related residential and commercial products, including carpet/rug (Beesoon et al., 2012; Harris et al., 2017), outdoor apparel (Hill et al., 2017), food packaging (Schaider et al., 2017), and canned food (Averina et al., 2018), might lead to exposure to PFHxS. That is, the consumption expenditure levels might also explain the trend of PFHxS levels along the Yangtze River.

4.2. Isomeric Fingerprints in Serum from Mianyang, Wuhan, and Hangzhou

Among exposure sources of PFASs, diet may account for up to 99% of the exposure for the general population (Shan et al., 2016). But it is difficult to explain the discrepancy in exposure levels among cities by the intake amount of diverse food because the distribution of PFASs in certain food ingredients is mainly related to the local environmental pollution characteristics. However, dietary habits are most likely to account for the isomeric profiles of PFASs in the human body because the isomeric fingerprints of certain PFAS produced by the same manufacturing technique remain stable. On the one hand, the patterns of PFAS isomers in the human body are affected by local production processes. On the other hand, various dietary habits may explain the main variation in the profiles of PFAS isomers in human serum because diverse foods show marked discrepancies in the accumulation of these isomers (Shan et al., 2016). The resident dietary structures in these places are illustrated in Figure S1.

4.2.1. Isomeric Fingerprints of PFOS

Regarding PFOS, the proportion of linear PFOS (*n*-PFOS%) of more than 70% in the present study coincided with previous studies on the serum of pregnant women from Wuhan (83%) (Chen

et al., 2017), Norway (78%) (Haug et al., 2011), and Edmonton, Canada (~80%) (Benskin et al., 2007). Besides, in plasma of pregnant women from south central Vietnam (81%) (Rylander et al., 2009), maternal whole blood (81.6%) and cord whole blood (79.7%) of pregnant women from Hubei Province, China (Zhao et al., 2017), women's serum (84.6%) from Fujian Province, China (Wang et al., 2018a), and cord serum (75.2%) of infants from Guangzhou, China (Zhang et al., 2017), *n*-PFOS% also exceeded 70%. It has been revealed that *n*-PFOS accumulated preferentially (Fang et al., 2016) but eliminated slower (Chen et al., 2015) than *br*-PFOS in carp, which might lead to the enrichment of *n*-PFOS. In human bodies, *br*-PFOS showed higher transplacental transfer efficiencies (Beesoon and Martin, 2015) and excretion efficiencies (Zhang et al., 2013b) than *n*-PFOS, which may account for the high *n*-PFOS% in the maternal serum of the present study.

The priority of food in accumulating *n*-PFOS follows the order of fish > meat > vegetables (Shan et al., 2016). Different dietary structures may be responsible for the differences in isomeric fingerprints in serum among Mianyang, Wuhan, and Hangzhou. As shown in Figure S1, Hubei has the highest vegetable intake, but its fish intake and meat intake were both lower than those of Hangzhou, so its *n*-PFOS% was supposed to be lower than that of Hangzhou. The total intake of fish and meat in Hubei was lower than that in Mianyang, while the intake of vegetables in Hubei surpassed that in Mianyang, so *n*-PFOS% in Wuhan was also proposed to be lower. Although fish intake in Hangzhou was much higher than that in Mianyang, so was vegetable intake, which probably explained why no large difference in *n*-PFOS% in serum was found between Hangzhou and Mianyang.

4.2.2. Isomeric Fingerprints of PFOA

Unlike PFOS which has only one production process, PFOA has two production processes, ECF and telomerization. Therefore, the isomer profile of PFOA in serum is first affected by local

production processes which decided the isomeric profiles of contamination background and, second, by dietary habits that affect the extent of exposure to different isomers.

As shown in Figure 2, the *n*-PFOA% values in Hangzhou (97–98%) were very close to those in telomerization products (100%). High *n*-PFOA% values in maternal or cord blood were also found in Fujian Province (99.8%) (Wang et al., 2018a), Guangzhou (98.7%) (Zhang et al., 2017), and Tianjin (99.0%), China (Jiang et al., 2014), as well as in Vancouver (97.8–98.1%), Canada (Beesoon et al., 2011). The use of telomerization as well as the preferential exclusion of branched PFOA from human bodies (Zhang et al., 2013b) might contribute to these high percentages of *n*-PFOA.

The *n*-PFOA% values in Mianyang (92–93%) and Wuhan (89–90%) were between those of ECF (78%) and telomerization products (100%). Such low *n*-PFOA% was also reported in the maternal whole blood of Hubei Province (92.8%), China (Zhao et al., 2017). It is possible that both processes have been used in Mianyang and Wuhan. According to a study on PFOA isomers in food from the same city, *br*-PFOA was rarely detected in meat and vegetables compared to fish, indicating that *br*-PFOA in serum was mainly derived from the intake of fish (Shan et al., 2016). The daily consumption of fish in Hubei Province was higher than that in Sichuan Province, so it was reasonable to find that *br*-PFOA% in Wuhan correspondingly surpassed that in Mianyang.

4.2.3. Isomeric Fingerprints of PFHxS

Studies on isomers of PFHxS are very limited, especially regarding human exposure. A previous study on the serum of occupational workers in a fluorochemical manufactory in China reported that the linear isomer of PFHxS accounted for 92.7% of the total PFHxS (Gao et al., 2015) which was close to the proportions of linear PFHxS (*n*-PFHxS%) in the serum of Mianyang (90%) and Hangzhou (96%) in the present study.

4.3. Transplacental Transfer of PFAS Isomers from Mothers to Infants

In the current study, the average R_{CM} values of ΣPFOS (0.38), ΣPFOA (0.83), and ΣPFHxS (0.55) were less than 1, suggesting that the placenta barrier partially blocks these contaminants from transferring into fetuses. Consistent with our findings, most reported mean/median values of R_{CM} for PFOS, PFOA, and PFHxS were less than 1 (Cariou et al., 2015; Chen et al., 2017; Eryasa et al., 2019; Fromme et al., 2010; Gao et al., 2019; Kim et al., 2011a; Lee et al., 2013; Liu et al., 2011; Needham et al., 2011; Pan et al., 2017; Wang et al., 2019; Yang et al., 2016), while some other studies reported that the R_{CM} values of PFOA exceeded 1 (Kim et al., 2011b; Li et al., 2020; Midasch et al., 2007; Ode et al., 2013). The reason for controversial reports on PFOA R_{CM} in literature was unclear before. Nevertheless, according to our new findings, one of the reasons may be that the transplacental transfer efficiency of PFOA is closer to 1, and its R_{CM} increased with decreasing PFOA concentration (Table 1).

The significant associations of maternal and cord serum for the concentrations of 1*m*-PFOS, 4*m*-PFOS, 3+5*m*-PFOS, *n*-PFOS, *iso*-PFOS, *n*-PFOA, *iso*-PFOA, *n*-PFHxS, and *br*-PFHxS indicated the transplacental transfer of PFAS isomers. To our knowledge, only three studies have investigated the transplacental transfer of individual isomers of PFOS, PFOA, or PFHxS. Among these three studies, two focused on serum (Beesoon et al., 2011; Chen et al., 2017), and one focused on whole blood (Zhao et al., 2017). The median R_{CM} of PFOS isomers in these three studies were shown in Table S10. It is apparent that the R_{CM} values of PFOS isomers in our study on serum were very close to those reported studies on serum but are approximately twice as high as those reported in the study on whole blood. This may be because the packed cell volume (PCV) of newborns (0.60) is greater than that of pregnant women (0.38) (Hanssen et al., 2013), and PFOS partitioned more in serum/plasma than in blood cells (Jin et al., 2016).

Interestingly, the rank order of R_{CM} in the present study (PFOS: 1*m* > 4*m* > 3+5*m* > *n* > *iso*, PFOA: *iso* > *n*) matched quite well with the sequence of binding affinities between the total protein in human serum and PFAS isomers (PFOS: 4*m* < 3+5*m* < *n* < *iso* < 1*m*, PFOA: *iso* < *n*, according to median values) (Beesoon and Martin, 2015), with the exception of 1*m*-PFOS. This supports that the binding affinity with serum proteins is an important factor affecting the transplacental transfer of PFAS isomers. The more PFAS-protein complexes there were, the fewer free PFASs in the serum crossed the placental barrier. The equilibrium dissociation constants of serum protein-PFAS complexes were positively correlated with the placental transfer efficiency of PFASs (Gao et al., 2019).

The transplacental transfer process is expected to be a bidirectional exchange, including two opposite directions of PFASs from maternal serum to cord serum and from cord serum to maternal serum. To analyze the process, we assume the corresponding transfer velocities are v_{mc} and v_{cm}, respectively, which will be equal at the equilibrium state. When the concentrations of PFASs on one side increase, more free PFASs will be able to cross the placenta. Correspondingly, the velocity of transferring these compounds from this side to the other should also increase and become closer to its saturation. In our present study, the significant associations between R_{CM} and $C_{maternal\ serum}$ rather than between R_{CM} and $C_{cord\ serum}$ elicited that the R_{CM} of 1*m*-PFOS, 4*m*-PFOS, *n*-PFOS, *iso*-PFOS, ΣPFOS, and ΣPFAS was mainly limited by v_{mc} rather than by v_{cm}. That is, v_{mc} is closer to its saturation than v_{cm}. In other words, the higher the PFAS levels in maternal serum, the more saturated the transfer ability of PFASs from the maternal side to the fetal side, while the ability to discharge PFASs from the fetal side is relatively unrestricted. In conclusion, it is likely that the stronger transfer abilities of transporters of PFASs from the infant side to the maternal side make the overall transplacental transfer efficiency (R_{CM}) decrease with increasing $C_{maternal\ serum}$. The discrepancy of transfer abilities may be due to the expression and number of transport proteins

for the two sides. Besides, further studies on the binding affinities between PFAS isomers and transport proteins in two sides of placentae will be helpful to understand transplacental transfer mechanisms.

5. Significance and limitation

The significance of this study can be summarized in 4 aspects. (1) The inter-regional comparison of human exposure levels and isomeric fingerprints provides important information for the regulation of specific PFASs and/or manufacturing processes in these cities in China. (2) Previous studies on human exposure pathways of PFASs usually focused on food, drinking water, air, and dust. Few studies have paid attention to the exposure pathway of consumer products. The present finding on the relationship between cities' consumption expenditure levels and 'residents' PFAS exposures emphasizes such a source of exposure to PFASs. (3) We captured specific isomers, not just total PFOA, PFOS, or PFHxS. This relatively avoids under- or over-estimating the effect of maternal exposure to PFASs, and allows us to shift our interest towards specific isomers. (4) Furthermore, the new finding on the associations of transplacental transfer efficiencies with PFAS concentrations in maternal and cord serum helps us better understand the transplacental transfer mechanism of these contaminants.

While the number of sampling sites was limited, a study on pregnant women in a large-scale watershed in the same country is still valuable because it is rare, representative, and inspiring. Based on our findings, further studies encompassing more sample sites and larger sample sizes in the same sampling time will be useful to depict a more representative pattern along the Yangtze River. Since PFASs may be used in intraocular surgery, in vivo oxygen delivery, plastic surgery, and other medical procedures, future investigations need to focus on participants' related disease

459 history and exclude these interfering factors. To detect isomer-specific PFASs, the instrumental
460 analysis method we used has high sensitivity but lengthy run time, which is beneficial for small
461 research but pose a limitation when used in large research with numerous samples.

462 **Conflict of interest**

463 The authors declare no competing financial interest.

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471 **Appendix A. Supplementary data**

472 Additional information including supplemental figures (Figures S1-S2) and supplemental
473 tables (Tables S1−S10).

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701

Table 1. Spearman Rank Correlation Coefficients between concentrations and transplacental transfer efficiencies of isomer-specific and total PFOS, PFOA, and PFHxS in Mianyang and Hangzhou.

	$R_{CM} - C_{maternal\ serum}$		$R_{CM} - C_{cord\ serum}$	
	Correlation Coefficient	Sig. (2-tailed)	Correlation Coefficient	Sig. (2-tailed)
1*m*-PFOS	-0.506**	< 0.001	-0.212	0.078
4*m*-PFOS	-0.638**	< 0.001	0.053	0.797
3+5*m*-PFOS	-0.244	0.058	0.194	0.133
n-PFOS	-0.450**	< 0.001	0.026	0.829
iso-PFOS	-0.495**	< 0.001	0.031	0.824
n-PFOA	-0.491**	< 0.001	-0.293*	0.013
iso-PFOA	-0.189	0.292	0.328	0.062
n-PFHxS	-0.585**	< 0.001	-0.412**	0.001
br-PFHxS	-0.687**	< 0.001	-0.376*	0.010
ΣPFOS	-0.468**	< 0.001	-0.039	0.742
ΣPFOA	-0.518**	< 0.001	-0.320**	0.006
ΣPFHxS	-0.610**	< 0.001	-0.389**	0.001
ΣPFAS	-0.373**	0.001	-0.103	0.389

* The significance level is 0.05 (2-tailed).

** The significance level is 0.01 (2-tailed).

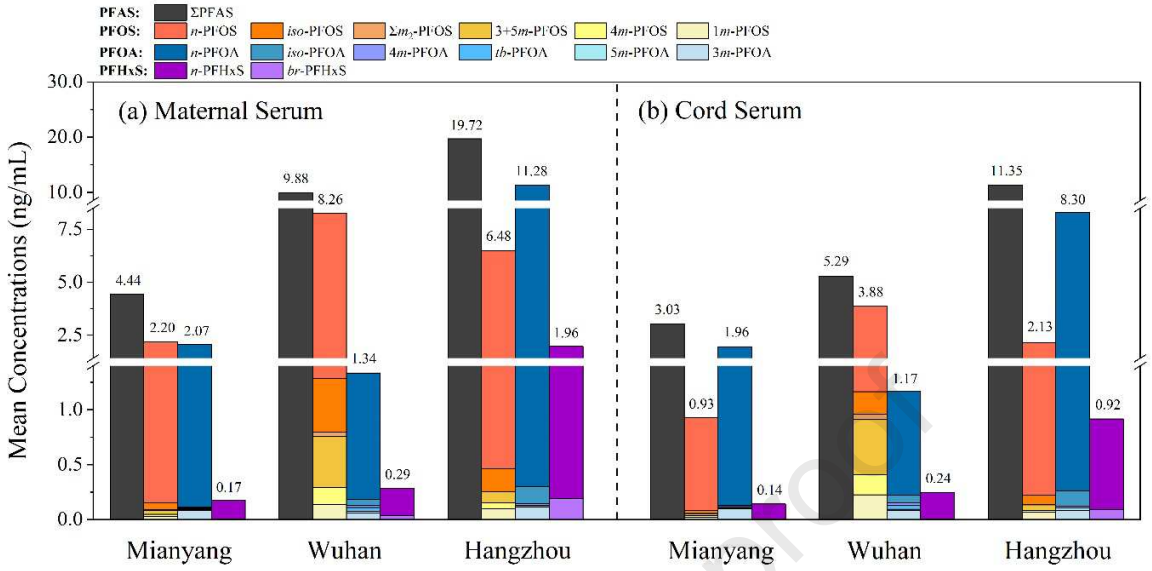
Figure Legend

Figure 1. The average concentrations of ΣPFAS and isomers of PFOS, PFOA, and PFHxS in maternal and cord serum in Mianyang, Wuhan, and Hangzhou.

Figure 2. Isomer compositions of PFOS, PFOA, and PFHxS in maternal serum and cord serum form Mianyang, Wuhan, and Hangzhou.

Figure 3. Transplacental transfer efficiencies (n = 72) of isomer-specific PFOS, PFOA, and PFHxS.

Notes: Original data are from Hangzhou and Mianyang. The square and the horizontal line in each box represents the mean and median, respectively. The bottom and top edges of each box represent the 25th and 75th percentiles, respectively. Whiskers represent the 95th and 5th percentiles. The circles below or above the whiskers indicate outlier values.



719

720 **Figure 1**

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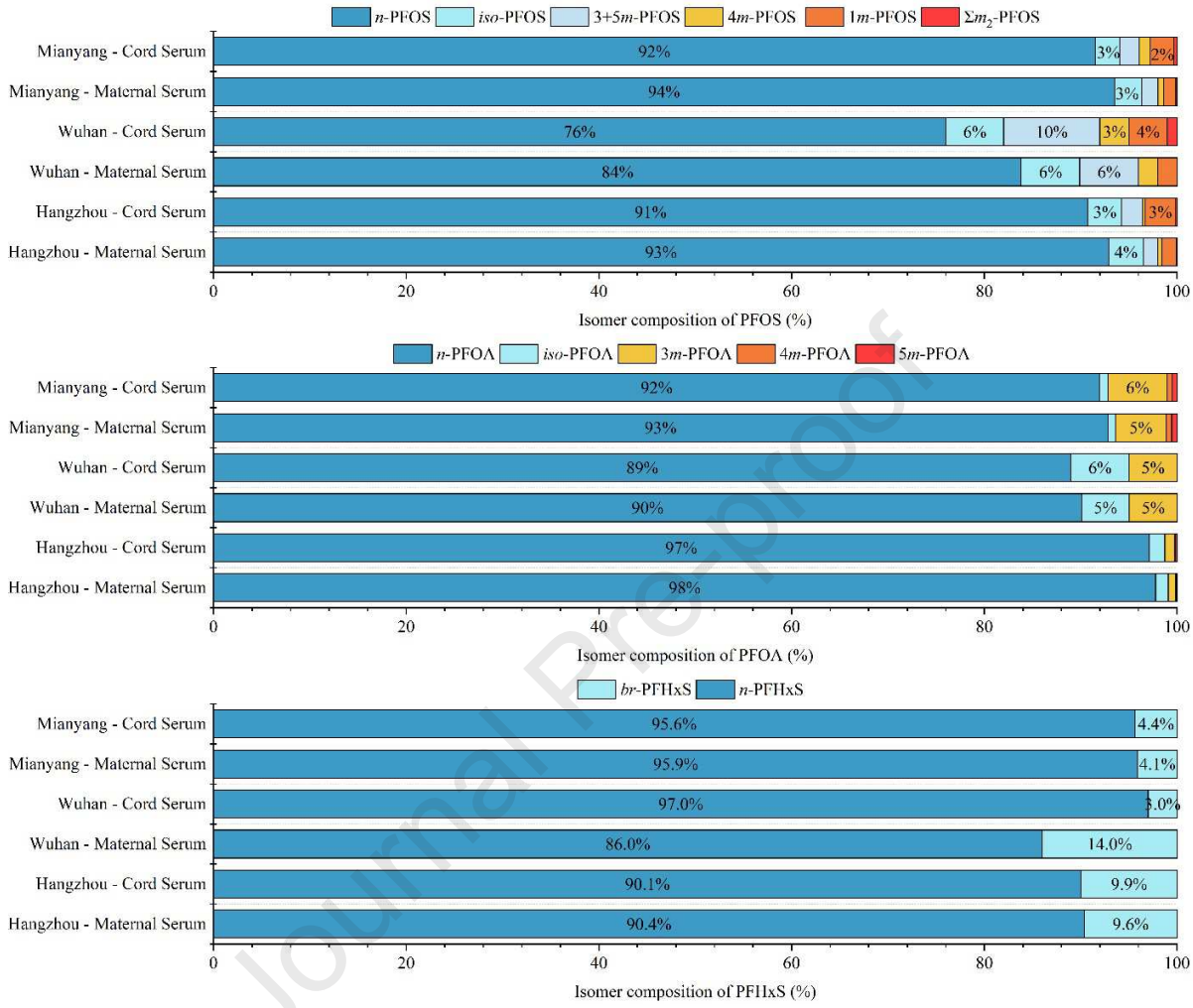
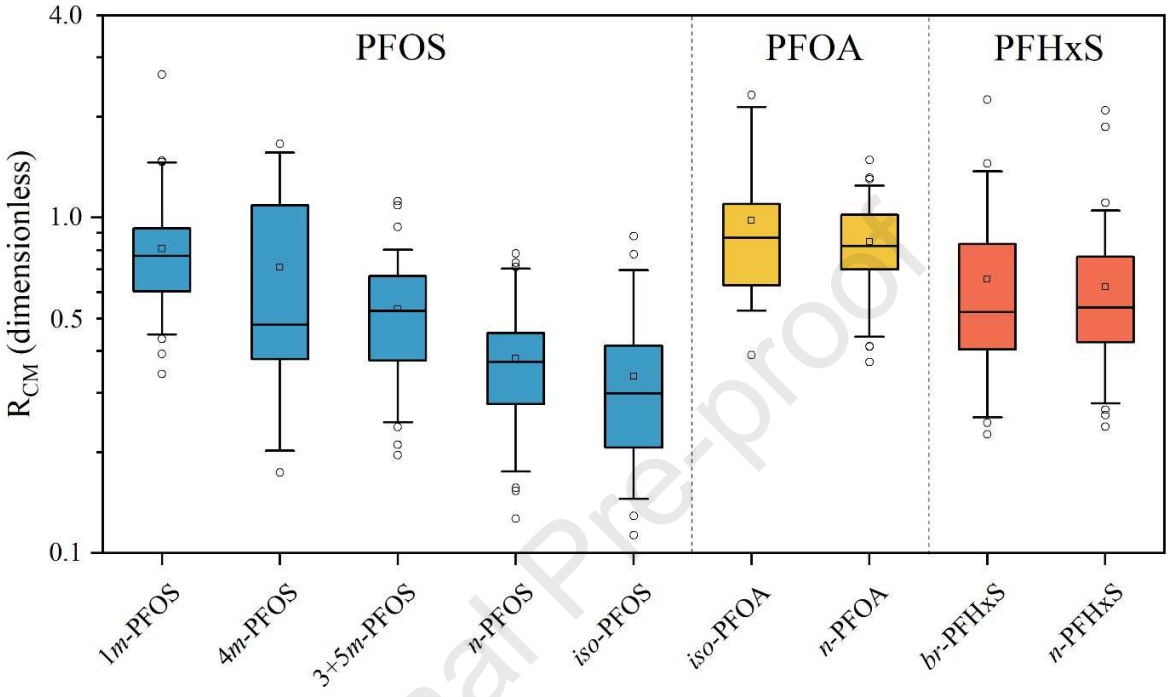

n-PFOS
iso-PFOS
3+5m-PFOS
4m-PFOS
1m-PFOS
Σm2-PFOS
Mianyang - Cord Serum
Mianyang - Maternal Serum
Wuhan - Cord Serum
Wuhan - Maternal Serum
Hangzhou - Cord Serum
Hangzhou - Maternal Serum
92%
3%
2%
94%
3%
76%
6%
10%
3%
4%
84%
6%
6%
91%
3%
3%
93%
4%
0
20
40
60
80
100
Isomer composition of PFOS (%)
n-PFOA
iso-PFOA
3m-PFOA
4m-PFOA
5m-PFOA
92%
6%
93%
5%
89%
6%
5%
90%
5%
5%
97%
98%
Isomer composition of PFOA (%)
br-PFHxS
n-PFHxS
95.6%
4.4%
95.9%
4.1%
97.0%
3.0%
86.0%
14.0%
90.1%
9.9%
90.4%
9.6%
Isomer composition of PFHxS (%)

Figure 2



728

729 **Figure 3**

730

- Prenatal PFAS exposure was highest in Hangzhou, followed by Wuhan and then Mianyang.
- Hangzhou had the highest ΣPFOA and ΣPFHxS, while Wuhan had the highest ΣPFOS level.
- The percentages of linear PFOS and PFOA in serum exceeded those in ECF products.
- PFAS isomers in serum were affected by production processes and dietary habits.
- Transplacental transfer efficiencies decreased with rising PFASs in maternal serum.

Declaration of interests

X The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: